



## Editorial

## Developmental, sexual and reproductive neuroendocrinology: Historical, clinical and ethical considerations

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## ABSTRACT

Different milestones have marked the development of the field of neuroendocrinology. This is an essay in which a new direction is proposed; one in which the field is marked more by a concern for ethical considerations than experimental procedures. Among the primary concerns is the need for a national registry for intersex and transsexual cases to follow how they are managed and to assess the long-term results. As in Europe, the data in the registries should be available to qualified and certified researchers and clinicians for analysis. A secondary focus is on the surgery often imposed in cases of intersex. Many current procedures have been found to have negative effects. The overall aim is to provide better management and treatment. Other topics are offered for ethical consideration.

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## 1. Introduction

The field of neuroendocrinology has had its share of exciting milestones opening up new areas for development. To my mind, considering the understanding of sexual/reproductive behavior, there are several that stand out. The most salient and earliest discoveries were obviously prehistoric. Probably from the early history of humans working with domesticated animals, it came to be known, that castration leads to an animal's increased docility and decrease in sexual drive as well as loss of reproductive function. Human reaction to the loss of testes, the creation of eunuchs, also occurred prehistorically, and most likely came soon after awareness of its animal effects. For humans the loss of reproductive function was assured; the effect of castration on sexual behavior was less so.

An historic milestone keeping with this theme occurred in 1849 when A.A. Berthold, using male chickens, showed that the testes were crucial to male total development [16]. He did this by castrating six male chicks before maturity. Two were completely castrated, two were hemi-castrated and two had testes that were transplanted between them. Those that had both testes removed developed into capons with the appearance and behavior typical of hens rather than roosters. Development in the two in which a single testes remained, and the two with transplanted testes, seemed to progress normally. These four developed comb, wattles, feathers and aggressive and sexual behaviors typical of roosters. This demonstrated the importance of the gonads as organs crucial for the development of both physical and behavioral characteristics.

The work of Steinach, in a series of experiments, provided consideration for a third significant historic milestone [116]. With the introduction of transplanted ovaries and testes into castrated guinea pigs, the basic differentiation of sex related morphology and behavior of an animal was shown dependent on the gonad's sex, not the animal's sex. When Steinach implanted an ovary into a prepubertal castrated male, it induced development of typical female adult appearance and reproductive behavior. In a comparable way a testes transplanted into a prepubertal female, induced in her, somatic and behavioral characteristics of an adult male. As Steinach said, this demonstrates "gonads are sex specific...The glands and not the nerves develop physical and psychic sex characteristics [116] p. 67."

The work of Phoenix et al. [97] has my vote as a fourth most significant milestone. Considering the neuroendocrinology of sexual differentiation and development, the experiments of these investigators basically established the *organization-activation* hypothesis. This showed that the adult sexual behaviors of animals could be significantly *organized* by prenatal testicular (androgenic) events that would later be *activated* by these same gonadal hormones. In other words, their work showed that it was crucial gonadal hormones introduced prenatally, more than features of rearing, which strongly structure postnatal adult behavior. And these findings, over the subsequent years, have been found to apply for humans as they do for other species [30,32]. Essentially the Phoenix et al. research might be considered a culmination and crucial cap to the preceding milestones mentioned.

A fifth benchmark is best noted by a composite analysis of the accumulating scientific genetic, endocrine, clinical and general social findings of many investigators that reversed a four-decade miscalculation. This milestone notes the recognition that one's psychosexual nature, rather than being simply a function of rearing or environmental influences, is instead biased at birth. This transition did not come easily (see below).

Considering the significance and breadth of this fifth milestone I propose the field of neuroendocrinology consider a new focus. And this new direction might be considered a sixth milestone. Whether it would be historic or not only time will tell. This turn in direction would be marked, as was the last milestone, not so much by a single experiment or even a series of them. I propose a new Frontier noted more by its *focus* rather than methodology. And this article is an essay in this cause. I suggest a broad attention to and consideration of the philosophical and ethical ramifications of neural-hormone interactions; many associated with the findings of the fifth benchmark. My own particular interest is primarily in regard to those relations associated with sexual differentiation and sexual behaviors. These interplays are fraught with ethical issues currently and will most probably increasingly be so in the future. But I suggest the focus be much broader. An enhanced understanding of clinical and general ethical considerations associated with the field can mark this frontier. There are many major issues that deserve attention, but also a host of smaller ones.

## 2. Registry

To illustrate, I will direct attention to two specific issues I consider of major importance and then call notice to some others that might be considered significant. The first matter is related to the practical ethics of having available, to qualified clinicians and researchers, the records and data of experimental and clinical findings relating to intersex conditions. The majority of intersex conditions are variant products of genetic and endocrine interactions where babies are born with various combinations of male and female features. The genitalia of intersexed infants might be ambiguous and not clearly male or female. Such individuals, depending upon the specific condition, need to contend with greater or lesser somatic and neural-behavioral features. The second matter is related to potential surgical ramifications of intersex syndromes. Currently there is no consistency in how these cases are clinically managed or evaluated. Their treatment can have neuroendocrinological significance. Both of these matters are ethically sensitive. There is much to be gained, and little to be lost, by access to relevant information on how these conditions are variously managed, and the long-term outcome of these management protocols.

## 3. National registries

In 1992 the US congress established a national cancer registry system where states were to collect, manage and analyze data about any cancer cases within their jurisdiction. These cases were to be reported to a central registry managed by the Centers for Disease Control and Prevention (CDC) [92]. These registries, and their contained data, are used to guide planning and evaluation of cancer management and treatment programs. Presently, in the United States, as they have been doing for the last two decades, cancer registrars in every state capture a complete summary of history, diagnosis, treatment, and status for cancer patients. Such a registry, with the accumulated data, allows for continual evaluations that lead to improvements in medical care by comparing details of management and therapies for each type of cancer. The registry thus offers an opportunity for enhanced treatment and support techniques to be recognized and developed. Certainly the proposed registry of patients with different intersex conditions, just as the many types of cancer were considered, should include all of the major varieties of DSD (Differences in Sex Development)<sup>1</sup> and

should prove of positive value similar to the cancer data trove. The NIH (National Institutes of Health) can maintain this register.

In Europe such a registry has already been established. Entitled the European DSD Registry it endeavors to collect data on patients with different varieties of intersex syndromes. The organizing body for the registry recognized “there is a large variation in how these patients are managed...across the world...and there are enormous gaps in our knowledge about the etiology of these conditions and the long term-outcome in adults with these conditions [1,2,48].” Scrutinized by ethics advisors, all appropriate safeguards have been incorporated in the establishment of the registry and maintenance and handling of the recorded data [48]. Security, ethics and information governance are cornerstones of the registry infrastructure and this should hold as well for any US database. Such a registry, as in Europe, should be open and available only to established and certified researchers and clinical partners. A protocol for the establishment for a research database has been established [1,2].

As it currently exists different physicians treat identical intersex conditions in different ways. Too often management programs are based on anecdotal accounts rather than evidence-based medicine. For instance individuals with Klinefelter syndrome (KS), of any variety, are almost routinely given testosterone or encouraged in its use [21,64]. And, any person found with large breast development, is prompted to get a mastectomy. This treatment might be appropriate for the majority but for at least a minority among this population it can be disastrous. Rarely are candidates for KS treatment interviewed regarding their gender preference or psychosexual interests. It is usually taken for granted that all will desire an identity as male and be gynephilic. A not small percentage of individuals with Klinefelter's syndrome, however, rebel against their management and elect to live as women despite having suffered from an imposed masculinization.<sup>2</sup> Individuals with KS have even born children [107]. Many regret their breast removal or breast reduction surgery and other aspects of their induced enhanced masculinization [44,78,95]. Others, with Klinefelter's syndrome, while not fully transitioning to live as women, prefer to live androgynously and without testosterone imposition [50]. And certainly there are those with KS who live as gay males [17,63,119]. Parkinson, in cases of KS, pleads “for careful assessment of gender identity before launching on physical treatments [95].” How frequently masculinizing treatments are imposed, with either positive or negative effects, is unknown since few long-term public records are published or otherwise made available.

The management of cases of androgen insensitivity syndrome (AIS) also has its unknowns. While it is true that those with the complete AIS condition most often prefer to live as women [120,127], this is not equally true for all those with the partial condition [44]. Some minority of those with partial AIS will elect to live as males and yet often have had their testes removed in a prophylactic effort by their physicians to prevent future testicular tumors.<sup>3</sup> Such men are angry that they were brought up as girls and are particularly distressed that they were, without their knowledge, and often without their or their parents' informed consent, at an early age, castrated and subjected to vaginal reconstructive surgery.<sup>4</sup> And then, from puberty on, were given estrogens to feminize them

<sup>2</sup> Perhaps the most famous of such individuals is Carolyn Cossy, who appeared as a female James Bond movie character. Her chromosome complement was XXXY. Raised as a male, she elected to switch to live as a woman [24]. She is not unique.

<sup>3</sup> Testicular cancer accounts for only 1% of all cancers in men in the United States; about 8000 men each year [88]. It is most often seen in men between the ages of 20 and 39. Since the incidence of tumors in such gonads is particularly low before the second decade, why is castration thought justified? No one seriously considers prophylactic removal of breasts in women even though the lifetime incidence of breast cancer is a significant 1 in 8 [62].

<sup>4</sup> The whole issue of informed consent deserves review. In the past this has often been truncated for the clinicians comfort and convenience [68,128].

<sup>1</sup> I refuse to use the acronym DSD to refer to Disorders of Sex Development as suggested by Hughes et al. [61]. The majority of persons with these conditions also hold this feeling as do intersex groups [35,41,58,122]. Referring to DSD as Differences maintains the accepted abbreviation without imparting stigma or negativism.

somatically. Without their gonads such individuals are forced to take medicinal steroids the remainder of their lives.

Often, further complicating matters, the early removal of their gonads is without an honest explanation of the rationale for the procedure or without fully informed consent received from their parents. Actually there is no need for early removal since tumorigenesis is rare prior to puberty and patients most often want to be, and deserve to be, involved in the decision-making of any potential or actual castration. Watchful waiting would seem to be the preferred ethical course. Analysis of accurate long-term records can tell clinicians and patients of the future which procedure is better under different circumstances and, certainly, unneeded surgery would be prevented. Untoward treatment incidents in the management of persons with DSD still occur. Fortunately, mistakes are increasingly being recognized and stopped and admissions of error have started [3].<sup>5</sup>

Even treatment for the most common intersex condition, congenital adrenal hyperplasia (CAH), is not yet standardized or uniform. Individuals with this condition, male or female, must replace cortisol, and occasionally the medical treatment for females is itself different from that of males. Currently there are several types of cortisol replacement treatments. Different replacement drugs are used and they have different characteristics. Some are short acting while others are comparatively long acting. The actual dose needed each day for each individual may differ, due to the variation in body size, different rates of absorption in the bowel, and other factors including patient compliance.<sup>6</sup> The wide variation in individual needs for each patient makes it especially apparent that a large accumulation of data would facilitate extraction of the best treatment methods for dealing with variations of this condition.

Among the most contentious issue in regard to those with CAH involves XX females. Females with CAH are generally born with an enlarged clitoris and often a vagina that is atypically formed. Questions arise as to whether they should have genital surgery or not – it is often recommended [124]. Sometimes, dependent upon the degree of masculinization of the genitals, there is question of whether they should be reared as males or females. Not infrequently, for various reasons such as the disease's late onset, some will be reared as males [110] and some will request such assignment [34]. Recommendations as to the management of severely masculinized infants with CAH are controversial. When it was first suggested that severely masculinized females be raised as males [42] the idea was generally rejected [52]. Lately, however, the idea is being revived [59,66].

Regarding the management of infants with intersex conditions and ambiguous genitalia, David Diamond (no relation) and colleagues reported in 2006 on a survey they conducted of pediatric urologists [28]. They asked how these specialists would clinically deal with infants diagnosed with CAH. The respondents overwhelmingly favored female gender assignment for females with CAH even if they were extensively masculinized (Prader V). They recommended feminizing surgery – reducing the size of an enlarged clitoris – and considered that preservation of female fertility was of foremost importance and the masculinization of behaviors or inclinations, was of lesser importance. There was a great difference of opinion as to the age it would be best to do the surgery.

In that same survey Diamond et al. asked how these pediatric urologists might treat cases of cloacal exstrophy.<sup>7</sup> For a case involving a male with cloacal exstrophy, a condition in which all external genitalia might be absent, notwithstanding retention of the gonads, 70% of respondents recommended male assignment and 30% a female one.

These 70% and 30% figures, in themselves, are crucial. They represent a dramatic reversal of how male infants with cloacal exstrophy would have been assigned just a decade earlier. These males then would all have been assigned as females. From the 1950s until the late 1990s, while the academic world debated the roles of nature and nurture in sexual development, particularly in regard to gender identity and sexual orientation, the medical establishment held the belief that children were born psychosexually "undifferentiated." This mistaken belief was primarily predicated on the work of John Money and John and Joan Hampson. These clinicians, from the prestigious John Hopkins medical school, wrote "In place of a theory of instinctive masculinity or femininity which is innate, the evidence of hermaphroditism lends support to a conception that psychologically, sexuality is undifferentiated at birth and that it becomes differentiated as masculine or feminine in the course of the various experiences of growing up" [85] p. 320, and "It is more reasonable to suppose simply that, like hermaphrodites, all the human race follow the same pattern, namely, of psychological undifferentiation at birth" [82] p. 820.

To bolster this thesis, in the 1970s, Money began to publish a series of papers purporting to show that a typical boy baby, David Reimer – better known as John/Joan, was successfully adjusting to being reared as a girl following the traumatic loss of his penis [83,84,86,87].<sup>8</sup> Taken as "proof" this significantly enhanced physicians' belief regarding psychological undifferentiation at birth. In so accepting the Money and Hampson thesis, clinicians routinely treated infants on that basis even accepting it as a standard of practice. In 1996 the American Academy of Pediatrics (AAP), relying on the Money and Hampson work, published, "Research on children with ambiguous genitalia has shown that sexual identity is a function of social learning through differential responses of multiple individuals in the environment... For example, children whose genetic sexes are not clearly reflected in external genitalia (i.e., hermaphroditism) can be raised successfully as members of either sex if the process begins before the age of 2½ years. Therefore, a person's sexual body image is largely a function of socialization [96]."

So, while scholars in psychology, developmental biology, and other academic disciplines argued the relative influences of nature and nurture on psychosexual development, and incorporated in their thinking the implications of the organization–activation theory, it was not so among physicians. In general, these practitioners thought the Money and Hampson's findings gave them a practical and simple solution to their management of troublesome cases. They accepted that individuals were psychosexually undifferentiated at birth and, since the appearance of the genitalia was considered crucial, surgery could be done to "normalize" any genital ambiguity. In females any large clitoris would be reduced or removed. In males with less than an adequate penis, the approach would be sex reassignment to female with surgical castration and penectomy since it was easier to remake the perineum into a vulva and vagina than a functional penis. And strangely, against ba-

<sup>5</sup> As part of its Resolve Project, Advocates for Informed Choice (AIC), an organization working on behalf of intersexed persons, has begun to encourage and receive apologies for past destructive or harmful practices imposed on infants.

<sup>6</sup> Many people don't take medications regularly, readily or easily. And the time of diagnosis can be quite variable with many persons having "late-onset CAH."

<sup>7</sup> Although not an intersex condition, I think the registry should also include cases of cloacal exstrophy since many of the thoughts and techniques of management are similar.

<sup>8</sup> To maintain privacy the boy was not identified in any of Money's reports. In that vein, to refer to him and his case, Sigmundson and I referred to him as John/Joan indicating first his male status and then his female one [43]. David's penis had been burned off accidentally during a circumcision done with a cautery. Without a penis Money thought it more appropriate that he be raised as a girl. He convinced David's parents of this and they agreed [43].

sic principals of individualizing treatment, all cases of ambiguous genitalia, regardless of etiology, were managed by being painted with the same brush i.e. their treatment was dependent upon the size of the phallus [38]. This derived management philosophy and belief in psychosexual neutrality at birth, unfortunately spread throughout the medical world and essentially held from the 1970s. It still holds not only in less developed countries but in developed ones as well.<sup>9</sup>

Certainly this thesis of “undifferentiation at birth” did not go without challenge [20,27,33] p. 169, [106,131]. My 1965 critique, supported by evidence available at that time, argued that human beings were, from birth, predisposed or “biased” to act in certain ways and that their “behavior is a composite of prenatal and postnatal influences with the postnatal factors superimposed on a definite inherent sexuality.” Many articles since then have extended thinking on the development of sexual orientation, identity, and Intersexuality [30,31,32,36,38,40]. But, it wasn’t until 1997 that the “undifferentiation” belief was directly challenged and a belief in an infant’s inherent sexuality gained increasing acceptance.<sup>10</sup>

The year 1997 brought with it a report that the John/Joan case was not as originally described. Instead of satisfactorily accepting assignment as a girl, David was found to have continually fought against his imposed displeasing female life and had asserted and demonstrated from early on, behaviors more typically seen in boys. At the age of 14 David—unknowing of his history—brought things to a head when he threatened suicide unless he could live as a boy and develop as a man. Only then was he finally told of how he came to be raised as a girl [43].<sup>11</sup>

This 1997 publication in the Archives of Pediatric and Adolescent Medicine was directed at a clinical audience and strengthened by an accompanying editorial [103] that also introduced the reader to one of the editorial writer’s own similar cases. Reiner had reported on a male teenager, raised unequivocally from birth on as a girl, who announced herself to be a boy at the age of 14 [101]. The impact was immediate. Physicians began, for the first time, to seriously question their clinical practice of the previous several decades. And so too was the general public alerted to these findings by a front-page report in the New York Times. That article began “A classic case of a gruesome surgical accident and its consequences that was long used as evidence of the pliability of sexual identity turns out, in follow-up, to suggest the opposite: that a sense of being male or female is innate, immune to the interventions of doctors, therapists and parents [6].”

An invited plenary address at the 1998 annual conference of the American Academy of Pediatrics (AAP) soon followed. The presentation refuted the idea of psychosexual neutrality at birth and strengthened a theory of prenatal organization and subsequent activation [38]. The impact was immediate. A national conference called “Pediatric Gender Assignment – A critical Reappraisal” was called in Dallas, Texas in the spring of 1999. Since then the thinking

has increasingly shifted from a belief in an infant being sexually neutral or undifferentiated at birth to a belief that it is psychosexually biased at birth [30,32,128]. It is continuation of this profound shift in thinking about human development, reflected in the thinking found in Diamond et al.’s surveys, that deserves consideration as the fifth milestone. It must also be recognized that prenatal influences on subsequent human behaviors are continually being recognized [15,18,47,57,91,117].

Diamond et al. summarized, their survey findings of the significant difference in potential management approaches as important and critical. Currently it certainly seems most efficient and proper – and most ethical – to determine, as efficiently and safely as possible, how best to manage these situations. It would augur better for both the patient and clinician as well. The expressed dramatic difference of opinion, regarding the surgical intervention for cloacal exstrophy, allows for a potential failure rate of 30% at best and a failure rate of 70% at worst. It is wrong to allow such a lack of knowledge to continue. Analysis of data in a long-term registry of pertinent cases could help correct such lacunae in knowledge.<sup>12</sup>

We can readily imagine that if there are controversies or disagreement as to the management of these more common intersex conditions, it is recognized that differences in how to deal with other cases seen infrequently, such as true hermaphroditism, 5-alpha reductase deficiency, vaginal agenesis, mixed gonadal dysgenesis, and others intersex combinations, would provide real quandaries. Many physicians, parents and others, have called for more data [68,128].<sup>13</sup>

#### 4. Pro & con

Critics against a proposed registry argue that individuals with intersex conditions would prefer not to have themselves identified or have their personal matters available for review e.g., [93]. There is fear the information could become public and lead to stigmatization, or even abuse of various types. Such criticisms existed similarly when the cancer registry was first established. Cancer still retains aspect of stigmatization [26] and it was certainly worse two decades ago. Then too, there was concern that information in the registry might be leaked to the detriment of patients. Nothing like that has happened, and over the years it has become obvious that the contributions to the registry have enhanced the lives of many, since better management techniques have prevailed over those that were seen less efficacious [92].

It is envisioned that those persons with intersex conditions today would see the value of contributing the history of their clinical management for the future benefit of others. Certainly, safeguards against mishandling of such data, as provided for by the European registry, have to be assured. Some clinicians also might object to having their techniques and clinical practices exposed and subject to peer or legal review. This is understandable. Here again security must be assured and liability issues safeguarded. But, a registry over time would be able to indicate which practices should no longer be used or protected, if found wanting.

<sup>9</sup> The German Intersex support group Zwischengeschlect.org has, as this article is being written, publicly called for a cessation of the current treatment of intersexed infants as practiced in their country. They argue, “today at least 90% were (and still are!) submitted to on average multiple medically unnecessary surgical genital mutilations in early childhood, resulting in appallingly high risk of lifelong loss of genital sensation, physical pain and severe psychological trauma [132].” A parallel report documenting the intersexed community’s objection to their treatment has also been submitted to the United Nations.

<sup>10</sup> A British television production in 1980 [126], and a publication in 1982 [39] did signal that things were not going as smoothly as Money suggested for David. Psychiatrists caring for David indicated they did not think he was successfully developing as a female but they were ignored. The general physicians’ belief in “undifferentiation at birth” still held.

<sup>11</sup> The complete story of David Reimer’s ordeal and its overall significance medically, psychologically, and in relation to a wide range of life from feminism to intersexuality and its management, is told in the book “As Nature Made Him: The boy who was raised as a girl” by John Colapinto [22].

<sup>12</sup> A recent follow-up to the 2006 survey report was conducted in 2010. In this recent survey Diamond et al. found, 79% would recommend male assignment for a male with cloacal exstrophy [29]. That still leaves a discrepancy in treatment potential where one in five infants, those set to live as girls, could be misassigned.

<sup>13</sup> In the address to the American Academy of Pediatrics in 1998, at their annual convention, a call was made for long term follow up on intersex cases to be published from existing records [38]. This was followed the next year with a national call for such information [128]. While many individual reports have since been published they represent only a small fraction of the available cases dealt with by a handful of investigators. The need for a national registry remains; the call is already more than a decade old and often echoed by many.

## 5. Surgery

A specific aspect of the medical treatment for different types of intersex conditions revolves around infant genital surgeries. Many ethical matters are associated with such practices. My second major proposal is related to such procedures.

In a 1999 address to the American Academy of Pediatrics [38] guidelines for the treatment of individuals with different intersexed conditions were proposed [38,72]. The first of these was: *There should be a general moratorium on infant surgery when it is done without the consent of the patient.* This recommendation was not offered because it was known that these surgeries did harm. It was presented because, till that time, there had not been any research to show that such surgeries – mostly for cosmetic purposes – were either needed or of benefit. Today, there are many studies that show them to be harmful. Perhaps the most significantly found damaging were those surgeries imposed on males that were sex reassigned for different reasons; usually due to genital trauma, micropenis or cloacal exstrophy. These were instances where the penis was considered too small for appropriate male status. The best known of such instances is the John/Joan case mentioned above [22,43] but there now have been many instances recorded where males were reassigned and raised as girls and then rebelled to live as males [101,102]. Cases of micropenis are also currently recognized as not needing surgery or sex reassignment [100,127].

Currently sex reassessments are less common than in the past but genital surgery on persons with ambiguous genitalia, particularly females with CAH, is not only still practiced but has lately even been recommended. For instance “Endocrine Society” guidelines of 2010 state “Surgical guidelines emphasize early single-stage genital repair for severely virilized girls, performed by experienced surgeons [114].” This, advice is presented despite the negative findings, of many. Creighton (2004), for example, has found “in girls with ambiguous genitalia, vaginoplasty is commonly performed during the first year of life although the child will not menstruate for a further 10 or so years and is unlikely to be sexually active until after puberty. There is no good evidence it is justified.” And Alizai et al. (1999) reported, “The outcome of clitoral surgery was unsatisfactory (clitoral atrophy or prominent glans) in 6 girls, including 3 whose genitoplasty had been performed by 3 different specialist pediatric urologists. Additional vaginal surgery was necessary for normal comfortable intercourse in 13 [of 14] patients. Fibrosis and scarring were most evident in those who had undergone aggressive attempts at vaginal reconstruction in infancy [4].” Minto and others [79,80] echo similar expressions against early genital surgery on girls. Schober has stated “A reliable, successful genitoplasty procedure that can be performed early in childhood for either feminization or masculinization has not yet been developed [109].” Legal and ethical reasons against such cosmetic surgery on infants have been presented [12].

It is significant that these infant surgeries, even by supposedly specialist pediatric urologists, were found unsatisfactory. This highlights the importance and value of late-in-life follow-up studies and challenges the status quo. It seems more ethical to defer definitive reconstruction of the genitalia until after puberty. Then, the informed desire of the person himself or herself, can be incorporated into any treatment, and psychological issues surrounding sexuality and surgery can be addressed [12]. The presentation of informed consent would also then be more likely. Findings from the registry data pool can be evaluated to see, if indeed, any surgery has value and if so, how these advantages might be best achieved.

On the basis of current knowledge, it seems, that doctors should never ethically undertake surgery, especially without fully informed consent, unless there are disproportionate dangers associ-

ated with all of the other options.<sup>14</sup> Above all, do no harm. It would seem obvious that the presumption has always to be against surgery unless two types of evidence are at hand. Kipnis has written, “Honoring the beneficence element of medical ethics requires evidence that children who receive such treatment do well on a life-long basis and that children who fail to receive such treatment do badly [71].” Such data are not at hand regarding the adult recipients of these surgeries. Since cosmetic infant surgery for intersex conditions has not yet proved itself beneficial, it should never be done unless there is an expectation of ample compensating benefits. And certainly, it seems, the surgical reassignment of sex remains an experimental procedure that should never be done without proper clinical findings that justify the practice.

A further consideration, that is not inconsequential, is the cost of surgery compared to an option such as nonsurgical dilation. A recent study found the nonsurgical dilation approach to forming a vagina to be just as effective as the surgical one costing twenty times as much [108].

## 6. Transsexual

As recommended above for persons with intersex characteristics, there seems similar value in a registry being established for cases of transsexuality. Transsexuals are individuals classified as having gender identity dysphoria or gender identity disorder (GID)<sup>15</sup> [7]. These persons are noted to have apparently normal anatomy accompanied by a persistent desire to change from the gender assigned to them at birth. The treatment and management for individuals with this desire to switch gender is met with a variety of treatment modules, as are cases of intersex. Actually from my own clinical experiences [34,44], my own experimental research [54], and from the findings of others [51] I conclude that transsexuality is a form of intersexuality.

As with cases of intersex, the treatment modes for GID can be 180° apart. Some psychotherapists treat children who manifest gender dysphoria with methods of denial and restriction. They try to make them comfortable in the sex of their birth. Other therapists treat similar children with permissiveness and license, trying to help them adjust to their gender of choice [115]. Certainly it is of benefit to know, for these not-rare clinical conditions, which is the best treatment technique, which has the most likely chance of success, and which leads to the most satisfying outcome for the patient or client. Surely it is most ethical to discover and apply the best management techniques and dismiss the others.

Not only parents want to know what is best for children but so too do therapists [129,130]. Without appropriate resources clinicians and parents are relying, not on evidence-based medicine or techniques of best practice, but to hunches, anecdotes and limited knowledge or experience. Just as intersexed persons deserve better, those with transsexual and related conditions deserve better. And certainly clinicians of all sorts, from pediatricians, urologists, surgeons, psychologists and psychiatrists, deserve better.

Before going further a comment is warranted. Many people make a distinction between intersexuality and transsexuality. Much opposition to linking the groups often comes from intersexed individuals who think the association somehow diminishes their own situation in the public eye [105]. This is regrettable. Both of these sexual minorities are stigmatized in society and should be

<sup>14</sup> The informed consent referred to is obviously that of the child in question. And that, by necessity, means that he or she must be granted the time (age) and maturity to make that decision. The argument that parents should not make this decision for the child has been defended [11].

<sup>15</sup> I consider the term *disorder* equally as inappropriate here as with Sex Development. I think the different gender expressions seen are manifestations of natural variations to be expected in any large open population. GID, as a term, has a long and established history. DSD is a relatively new term.

allies in their fight against discrimination [111]. I believe that transsexuals are intersexed in their brains as others are or might be more obviously so in their gonads, genitals, hormonal character, receptors, enzymatic or chromosomal constitution. And it is this brain intersexuality that biases the person to assert his or her gender identity [13,30,37].

As one can vary in sexual orientation from 0 to 6 on a Kinsey scale [69,70], and can fluctuate in behavior during one's life, so too can one vary from I to VI on the Benjamin scale [14] demonstrating different degrees of a *trans* gender identity. This can be manifest by occasional cross-dressing to full-time transsexuality where a person lives 24/7 in a mode different from the way he or she was born and raised. And this gender identity can fluctuate in display from mild to intense during different times in one's life and in reaction to a variety of life experiences.

There are, certainly, differences between the groups. While most persons with standard intersex conditions regret any surgery that had been imposed on them and protest the practice [65], most transsexual persons welcome surgery [55]. Considering the management needs and desires of both groups, and determining the relative success of different methodologies, is, I think, the more ethical position. It is also ethical to consider the general medical needs of transsexuals since they are often the brunt of open discrimination for such services [55].

A registry established for the treatment and management of cases of transsexuality/GID, as the registry for intersexed individuals, should also be maintained for as long as possible. Children with manifestations of GID may remain as assigned for decades only to transition as adults; many after the age of 50 [23,49]. Recording the success or failure of different management techniques for different GID situations would obviously allow for analysis and improvement in treatment. There is, for example, critical debate as to the value of an imposed real life experience (RLE), how long it should be and whether it should serve as a test of sorts.

It is cogent to mention here that there are persons with strong cross-gender feelings that, for one reason or another, do not transition. This is not much different from those who are obviously intersexed, yet who elect not to change from existing conditions that they find distasteful or uncomfortable. As do many people in everyday society, persons refrain from following negative feelings in order to solve other life problems with which they have to contend. Probably the most crucial reason transsexuals do not get surgery and transition is their inability to afford the large expense [55]. In other regards, they evaluate whether or not the transition is worth the loss of family, religion, job, children, etc. [45].<sup>16</sup> Understanding the underlying character of these situations, in light of different treatment modes, would be of value. A long-term registry would help illuminate the clinical relevance of such situations.

After transition, many transsexuals as the majority of intersexed persons just prefer to remain in the "woodwork" and not be identified as different. They prefer life in "stealth" mode. This is understandable for them as for any person who elects not to be identified as different. However, it is anticipated that they too, as long as their privacy were assured, would understand and accept the value of having their records available in a research registry to help their future "siblings."

## 7. Other ethical issues

There is no shortage of other ethics-related matters associated with the field of neuroendocrinology and many are quite current. Consider the following:

### 7.1. Sexual orientation

As presently understood, sexual orientation is at least partially, if not mostly, induced by prenatal neuroendocrine events [9,10,30,32]. Would it be ethical to see if that can be modified in humans? Who would have to sanction it and could parents request such treatment for an embryo or fetus suspected of having been induced toward or away from homosexuality or heterosexuality? Debate on such questions is currently at issue [46].

### 7.2. Prenatal dexamethasone

Concern with sexual orientation is only one facet in considering cases of CAH. Clinicians, parents and others are often concerned with the masculinization of genitalia and behavior that accompanies CAH. Prenatal treatment with dexamethasone has been utilized to prevent genital masculinization with supposed success [89]. The ethics of such treatment is controversial and hotly debated [67,76,77,89,90,104,121]. The neuroendocrinological parameters of such treatments are largely unknown. Particularly of issue is the question of whether or not prenatal treatment of pregnant women, for the prevention of any type of masculinization, should be attempted at all [46–77]. In some regions it is reported as standard practice [113].

### 7.3. Informed consent

A clear and consistent definition and understanding for the meaning of "Informed consent" would seem to be ethical, laudable and obtainable. Considering all the different experimental protocols proposed for neuroendocrinological investigations how might such a full and meaningful adherence to a goal of fully informed consent be achieved? Many suggestions have been offered [5,8,56,73,75,99]. This obviously has legal ramifications when humans are involved.

### 7.4. Environmental pollutants

Environmentally there are a host of indications that animals, are turning up with ambiguous or modified genitalia. The British environmental group EcoTrust has reported "Males of species from each of the main classes of animals in the vertebrate sub-phylum (including bony fish, amphibians, reptiles, birds, and mammals) have been affected by chemicals in the environment, particularly chemicals with hormone disrupting properties... These [problems] include altered hormone levels, reduced number of sperm, genital deformities and deformities of other structures under sex hormonal influence [74]." This has provoked serious distress calls on behalf of several species such as polar bears and seals [25]. There is fear of these species going extinct. The same substances [94] also affect humans. Some of these pollutants might be byproducts of manufactured materials; others of it may be due to the release of metabolic remnants of non-degraded estrogens from contraceptive pills or other sources. How might such concerns be ethically dealt with? What about non-endocrine developmental disruptors such as phthalates [98] or PCBs and dioxins [125]? All of these have been implicated as serious environmental pollutants that can disrupt masculine development [118]. How are these best ethically dealt with? Should the field take a public stance on the issue?

<sup>16</sup> Because persons are willing to openly confront the social conflicts and difficulties involved in continuing to live a *trans* or intersex existence, I see them as only different in expression and character from others that do so by showing major open societal differences in sexual orientation, religion or other feature of their inherent physical or psychological biases. I think society should understand this characterization. I also think therapists and therapy, via the *Diagnostic and Statistical Manual* (DSM) of the American Psychiatric Association should reflect this possibility and potential. Similarly, I think a requirement that one undergo surgery to legally establish a gender change is unnecessarily onerous.

### 7.5. Disease mongering

There is a temptation among some groups to create and promote diseases that conceptually might or might not exist. An example of just one of these is “female sexual dysfunction.” Whether or not there is such a real entity is debatable [112,123]. Such a disease, if it actually exists, might be expected to have neurological and endocrine components [53]. How should neuroendocrinologists most efficiently deal with this phenomenon?

### 7.6. Doping

Much has been made of different kinds of “doping” in sports. What ethical considerations should be considered about any neuroendocrine facets of such practices? Are there legitimate occasions when the use of hormones, for non-medical use, might be acceptable? What about for personal bodybuilding as an example?

## 8. Discussion/conclusions

All of the issues presented have ethical, as well as practical, ramifications that at least warrant discussion if not resolution. To my mind the establishment of registries for cases of intersex and transsexual management and treatment offer the greatest opportunity for potential gain. The gain would be for patients and clinicians, researchers and subjects.

The registries can start from the files of those clinicians and researchers that have been in practice for a number of years. They should offer a body of data enough to, at least, help the organization and establishment of clinical and experiential review questions and data saving formats so that better and best practices can be extracted and evaluation facilitated.

Here are some examples of already known large files that would be appropriately placed in a national registry. Presently there are supposedly 600 cases in which dexamethasone has already been administrated in order to ameliorate the prenatal masculinizing effects of CAH [81]. With the proper safeguards for clinician and patients, an ethical use of such case records should be part of any registry of DSD patients. Similarly a personal series of over 600 cases of hypospadias has led one author to conclude that a two-stage operation for repair is better than a one-stage method [19]. These data too should be publically available for scrutiny and analysis. And as just another example, more than 600 cases with a Y aneuploidy (other than non-mosaic 47, XYY) were reviewed for phenotype/karyotype correlations. This review showed a major difference in reported phenotypes between postnatally and prenatally diagnosed cases of mosaicism [60]. All these cases could offer a rich information pool from which to gain at least a protocol for future investigation of clinical cases. They are offered here only as examples of large data sets that might easily be made available.

Surveillance is a key component of the core public health function of health assessment. Mandatory registration of intersex and transsexual cases and their management and outcomes should be required and maintained so that critical analysis of the data can lead to increased professional knowledge and enhanced management of differences in sex development and gender identity. This could help insure better future clinical health care; a fitting focus for a sixth milestone in the field of neuroendocrinology.

Claude Bernard, one of the most eminent of our scientific forefathers stressed the use of the scientific method in medicine. He dismissed many previous misconceptions, took little for granted, and relied on experimentation. We would do well to accept analytic scientific exploration of past practices and replace physicians and other clinicians over dependence on anecdote and case reports with data and critical analysis.

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